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EXAMINER	
FORD, VANESSA L	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/712,335	DE BOLD, ADOLFO J.	
	Examiner	Art Unit	
	VANESSA L. FORD	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/4/04, 12/28/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-21 filed on December 27, 2006 is acknowledged. Groups II and III claims 22 and 23, respectively are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being to a non-elected invention.

This application contains claim drawn to an invention nonelected with traverse in the reply filed on December 27, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The traversal is on the grounds that Groups I-III are not independent and distinct, therefore the examination of the entire application does not constitute a serious burden. These arguments have been fully considered but are not found to be persuasive for the reasons below:

First, the classification system has no statutory recognition whether inventions are independent and distinct. For example, each class and subclass is comprised of numerous completely independent and distinct patented inventions.

Second, MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term "distinct" is defined to mean that two or more subjects as disclosed are related, for example as product and method of use, etc., but are capable of separate

manufacture, use or sale as claimed, and are patentable over each (see MPEP 802.01). In the instant situation, the inventions of Groups I-III are drawn to distinct inventions which are separate products and methods capable of separate manufacture, use or sale as described in the previous Office Action.

Classification of the subject matter is merely one indication of the burdensome nature of the search. The literature search, particularly relevant in this art, is not co-extensive, because for example, Groups I, II and III are drawn to *different methods* which require *different endpoints*. Clearly different populations of subjects and different goals are involved with the examination of each Group of inventions. Therefore, different searches and issues are involved in the examination of each Group.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL. Claims 1-21 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Independent claim 1 is directed to a method of assisting in the diagnosis of cardiomyopathy, myocarditis or both, that arises as a result of an infection in a patient, comprising, obtaining a sample of a body fluid from the patient, and determining a level of a brain natriuretic peptide (BNP) or fragment thereof, atrial natriuretic peptide (ANF) or fragment thereof, or both BNP and a fragment thereof and ANF or fragment thereof, within the sample of body fluid and comparing the level of BNP, ANF or both BNP and ANF to the level of BNP, ANF or both BNP and ANF from a control group, wherein an increase in the level of BNP, ANF or both BNP and ANF in the sample, compared to the level of BNP, ANF or both BNP and ANF in the control group, is an indicator of a symptom of cardiomyopathy, mycarditis or both cardiomyopathy and mycarditis that arises as a result of an infection in a patient.

The claims are directed to a vast genus of fragments of ANF and BNP, fragments of the combination of ANF and BNP as well as fragments of the mature BNP, fragments of ProBNP, fragments of mature ANF and fragments of ProANF. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately

recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. To adequately describe the genus of ANF and BNP molecules, Applicant must adequately describe the antigenic determinants (immunoepitopes) of the claimed polypeptides.

The specification, however, does not disclose distinguishing and identifying features of a representative number of members of the genus of polypeptides to which the claims are drawn, such as a correlation between the structure of the immunoepitope and function so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of polypeptides. Moreover, the specification fails to disclose which amino acid residues are essential to the function of the immunoepitope or which amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent, or with which other amino acids, the non-essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. The specification fails to adequately describe at least a substantial number of members of the claimed genus of polypeptides capable of being used for a therapeutic purpose.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to

those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed.

See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.
The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has

Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan et al (*Nature Biotechnology 7: 936-937, 1999)*, defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of polypeptides capable of providing therapeutic purposes for example being used as a vaccine.. Consequently, because the

art is unpredictable, in accordance with the Guidelines, the description of immunoepitopes (antigenic determinants) is not deemed representative of the genus of polypeptides to which the claims refer. Hence, only sequences that meet the written description requirement are ANF and BNP.

Scope of Enablement

3. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of assisting in the diagnosis of cardiomyopathy, myocarditis or both, that arises as a result of an infection in a patient, comprising, obtaining a sample of a body fluid from the patient, and determining a level of a brain natriuretic peptide (BNP) or atrial natriuretic peptide (ANF) or both does not reasonably provide enablement a method of assisting in the diagnosis of cardiomyopathy, myocarditis or both, that arises as a result of an infection in a patient, comprising, obtaining a sample of a body fluid from the patient, and determining a level of a BNP fragments or ANF fragments or fragments of the combination of ANF and BNP as well as fragments of the mature BNP, fragments of ProBNP, fragments of mature ANF and fragments of ProANF.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Independent claim 1 is directed to a method of assisting in the diagnosis of cardiomyopathy, myocarditis or both, that arises as a result of an infection in a patient,

comprising, obtaining a sample of a body fluid from the patient, and determining a level of a brain natriuretic peptide (BNP) or fragment thereof, atrial natriuretic peptide (ANF) or fragment thereof, or both BNP and a fragment thereof and ANF or fragment thereof, within the sample of body fluid and comparing the level of BNP, ANF or both BNP and ANF to the level of BNP, ANF or both BNP and ANF from a control group, wherein an increase in the level of BNP, ANF or both BNP and ANF in the sample, compared to the level of BNP, ANF or both BNP and ANF in the control group, is an indicator of a symptom of cardiomyopathy, mycarditis or both cardiomyopathy and mycarditis that arises as a result of an infection in a patient.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

The claims are drawn to determining the levels of ANF and BNP in body fluids. However, Applicant has failed to disclose the structure of ANF and BNP fragments or fragments of the combination of ANF and BNP used in the claimed method. Protein chemistry is probably one of the most unpredictable areas of biotechnology. The effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al *(Science, 1990, 257:1306-1310)* teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is

the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are *critical* to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, as evidenced by Greenspan et al *(Nature Biotechnology 7: 936-937, 1999),* defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of a given immune reaction,

the specification, as filed, does not provide enablement for polypeptides (other than ANF and BNP) used in the claimed method.

There is no guidance provided in the specification with regard to how one would begin to choose fragments of ANF or BNP or fragments of ANF and BNP, fragments of the combination of ANF and BNP as well as fragments of the mature BNP, fragments of ProBNP, fragments of mature ANF and fragments of ProANF. The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- what fragments, can be made which the retain the biological activity if the intact protein; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choice is likely to be successful.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting ANF and BNP fragments or fragments of ANF and BNP, fragments of the combination of ANF and BNP as well as fragments of the mature BNP, fragments of ProBNP, fragments of mature ANF and fragments of ProANF having claimed the functional features, 3) the

relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptides that are fragments ANF and BNP in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of deletions or fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546 (Bd. Pat. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims. In view of all of the above, all polypeptides encompassed by the claimed invention do not satisfy the requirements of 35 U.S.C. 112 first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 11 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 11 recites "over a period of time…". This phrase is indefinite. What interval of time is Applicant referring ? Is Applicant referring to 2 minutes, 1 hour, 18 hours , 2 days, 6 months or etc.? Clarification/correction is required.

5. Claim 11 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 11 recites "more than two samples…". This phrase is indefinite. How many samples is Applicant referring? There is no upper limit as how many samples are required. Clarification/correction is required.

It should be noted that the Examiner is viewing ANP and ANF as the same atrial natriuretic peptide.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-3, 8-13 and 17-21 rejected under 35 U.S.C. 102(b) is anticipated by Lerman et al *(Lancet, May 1, 1993, Vol. 341, p. 1105-1109).*

Independent claim 1 is directed to a method of assisting in the diagnosis of cardiomyopathy, myocarditis or both, that arises as a result of an infection in a patient, comprising, obtaining a sample of a body fluid from the patient, and determining a level of a brain natriuretic peptide (BNP) or fragment thereof, atrial natriuretic peptide (ANF) or fragment thereof, or both BNP and a fragment thereof and ANF or fragment thereof, within the sample of body fluid and comparing the level of BNP, ANF or both BNP and ANF to the level of BNP, ANF or both BNP and ANF from a control group, wherein an increase in the level of BNP, ANF or both BNP and ANF in the sample, compared to the level of BNP, ANF or both BNP and ANF in the control group, is an indicator of a symptom of cardiomyopathy, mycarditis or both cardiomyopathy and mycarditis that arises as a result of an infection in a patient.

Lerman et al teach a method of determining atrial natriuretic peptide (ANP) levels in patients that are symptomless for left-ventricular dysfunction (see the Title and page 1105). Lerman et al teach that the left ventricle is an important determinant of the outcome of congestive heart failure (page 1105). Lerman et al teach that atrial natriuretic peptide is released as a C-terminal peptide and an N-terminal peptide (see page 1105). Lerman et al teach that plasma N-ANP concentrations are significantly

increased in patients with symptomless left-ventricular dysfunction and that this peptide can serve as a marker for diagnosis of such patients (page 1105). Lerman et al teach that blood samples were taken from each patient and analyzed (page 1107). Lerman et al teach that antibodies to ANP $_{1-25}$ were used for assay of the N-terminal form and to the ANP $_{99-126}$ for assay of the C-terminal form (page 1107). Lerman et al teach assays were performed using radioimmunoassays (page 1107). Lerman et al teach that N-ANP measurement could be used to identify patients with symptomless heart disease and permit more in depth study of the natural history of congestive heart failure (page 1108). Lerman et al anticipate the claimed method.

7. Claims 1-3, 8-16 and 20-21 rejected under 35 U.S.C. 102(b) is anticipated by Motwani et al *(Lancet, Vol,. 341, May 1, 1993, 1110-1113).*

Independent claim 1 is directed to a method of assisting in the diagnosis of cardiomyopathy, myocarditis or both, that arises as a result of an infection in a patient, comprising, obtaining a sample of a body fluid from the patient, and determining a level of a brain natriuretic peptide (BNP) or fragment thereof, atrial natriuretic peptide (ANF) or fragment thereof, or both BNP and a fragment thereof and ANF or fragment thereof, within the sample of body fluid and comparing the level of BNP, ANF or both BNP and ANF to the level of BNP, ANF or both BNP and ANF from a control group, wherein an increase in the level of BNP, ANF or both BNP and ANF in the sample, compared to the level of BNP, ANF or both BNP and ANF in the control group, is an indicator of a symptom of cardiomyopathy, mycarditis or both cardiomyopathy and mycarditis that

arises as a result of an infection in a patient.

Motwani et al teach a method of determining brain natriuretic peptide (BNP) levels in patients that have changes in ventricular function (page 1109). Motwani et al teach that plasma samples were taken from each patient in the study and assayed using radioimmunoassay (RIA) (page 1110). Motwani et al teach that anti-hBNP32 antibody was used in the study (page 1110). Motwani et al teach that in chronic heart failure, plasma BNP concentrations are substantially increased, the circulating concentration is proportional to the severity of heart failure (page 1111). Motwani et al teach that BNP is a unique marker of left-ventricular dysfunction at both early and late stages (pages 1111 and 1112). Motwani et al anticipate the claimed method.

8. Claims 1-3, 6-13, 17 and 19-20 are rejected under 35 U.S.C. 102(a) is anticipated by Puyo et al *(Regulatory Peptides, Vol. 105, May 15, 2002, p. 139-143)*.

Independent claim 1 is directed to a method of assisting in the diagnosis of cardiomyopathy, myocarditis or both, that arises as a result of an infection in a patient, comprising, obtaining a sample of a body fluid from the patient, and determining a level of a brain natriuretic peptide (BNP) or fragment thereof, atrial natriuretic peptide (ANF) or fragment thereof, or both BNP and a fragment thereof and ANF or fragment thereof, within the sample of body fluid and comparing the level of BNP, ANF or both BNP and ANF to the level of BNP, ANF or both BNP and ANF from a control group, wherein an increase in the level of BNP, ANF or both BNP and ANF in the sample, compared to the level of BNP, ANF or both BNP and ANF in the control group, is an indicator of a

symptom of cardiomyopathy, mycarditis or both cardiomyopathy and mycarditis that arises as a result of an infection in a patient.

Puyo et al teach a method of determining atrial natriuretic peptide (ANF) levels in patients that are myocardial comprised (the Title and page 139). Puyo et al teach that myocardial failure leads to increased ventricular production of ANF and BNP (page 139). Puyo et al teach that patients with chronic heart failure have high plasma concentration of both natriuretic peptides correlated with the extent of ventricular dysfunction (page 139). Puyo et al teach that Chagas' disease, one of the determinants of chronic heart failure and sudden cardiac death and is caused by a protozoan parasite *Trypanosoma cruzi* (page 139). Puyo et al teach that samples were taken from patients and plasma ANF was analyzed using radioimmunoassays (RIA) (page 140). Puyo et al teach that plasma ANF levels were elevated in patients with conduction defects and chronic heart failure of different origins (page 141). Puyo et al has demonstrated elevated plasma ANF levels in the acute but also in the chronic myocarditis induced by *T. cruzi* infection (page 142). Puyo et al anticipate the claimed method.

9. Claims 1-3, 6-13, 17 and 19-20 are rejected under 35 U.S.C. 102(b) is anticipated by Scaglione et al *(J Parasitol., Aug; 87(4):923-6)*.

Independent claim 1 is directed to a method of assisting in the diagnosis of cardiomyopathy, myocarditis or both, that arises as a result of an infection in a patient, comprising, obtaining a sample of a body fluid from the patient, and determining a level

of a brain natriuretic peptide (BNP) or fragment thereof, atrial natriuretic peptide (ANF) or fragment thereof, or both BNP and a fragment thereof and ANF or fragment thereof, within the sample of body fluid and comparing the level of BNP, ANF or both BNP and ANF to the level of BNP, ANF or both BNP and ANF from a control group, wherein an increase in the level of BNP, ANF or both BNP and ANF in the sample, compared to the level of BNP, ANF or both BNP and ANF in the control group, is an indicator of a symptom of cardiomyopathy, mycarditis or both cardiomyopathy and mycarditis that arises as a result of an infection in a patient.

Scaglione et al teach a method of determining atrial natriuretic peptide (ANF) levels in subjects have myocarditis produced by *Trypanosoma cruzi* infection (e.g. Chagas' disease)(see the Abstract). Scaglione et al teach that the highest plasma ANF levels were found in chronically infected could derived from the progressive failure of cardiac function (see the Abstract). Scaglione et al that plasma extraction and ANF radioimmunoassay (RIA) were performed on subjects (page 924). Scaglione et al teach that anti-rat ANF(99-126) were used in the assays (page 924). Scaglione et al anticipate the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-4, 8-13 and 17-21 are rejected under 35 U.S.C. 103(a) as patentable over Lerman et al *(Lancet, May 1, 1993, 1105-1109)* in view of Marumo et al *(Clinical Chem, 36/9, p. 1650-1653, 1990)*.

Independent claim 1 is directed to a method of assisting in the diagnosis of cardiomyopathy, myocarditis or both, that arises as a result of an infection in a patient, comprising, obtaining a sample of a body fluid from the patient, and determining a level of a brain natriuretic peptide (BNP) or fragment thereof, atrial natriuretic peptide (ANF) or fragment thereof, or both BNP and a fragment thereof and ANF or fragment thereof, within the sample of body fluid and comparing the level of BNP, ANF or both BNP and ANF to the level of BNP, ANF or both BNP and ANF from a control group, wherein an increase in the level of BNP, ANF or both BNP and ANF in the sample, compared to the level of BNP, ANF or both BNP and ANF in the control group, is an indicator of a symptom of cardiomyopathy, mycarditis or both cardiomyopathy and mycarditis that arises as a result of an infection in a patient and and dependent claim 4 is directed to the method of claim 1, wherein the body fluid comprises urine.

Lerman et al teach a method of determining atrial natriuretic peptide (ANP) levels in patients that are symptomless for left-ventricular dysfunction (see the Title and page 1105). Lerman et al teach that the left ventricle is an important determinant of the outcome of congestive heart failure (page 1105). Lerman et al teach that atrial natriuretic peptide is released as a C-terminal peptide and an N-terminal peptide (see page 1105). Lerman et al teach that plasma N-ANP concentrations are significantly increased in patients with symptomless left-ventricular dysfunction and that this peptide

can serve as a marker for diagnosis of such patients (page 1105). Lerman et al teach that blood samples were taken from each patient and analyzed (page 1107). Lerman et al teach that antibodies to ANP $_{1-25}$ were used for assay of the N-terminal form and to the ANP $_{99-126}$ for assay of the C-terminal form (page 1107). Lerman et al teach assays were performed using radioimmunoassays (page 1107). Lerman et al teach that N-ANP measurement could be used to identify patients with symptomless heart disease and permit more in depth study of the natural history of congestive heart failure (page 1108).

Lerman et al do not teach the method of claim 1, wherein the body fluid comprises urine.

Marumo et al (1990) teach that atrial natriuretic peptide (ANP) is present in the urine (see the Title and page 1650).

It would have been *prima facie* obvious at the time the invention was made to substitute the body fluid sample, plasma for the body fluid sample, urine in a method of assisting in the diagnosis of cardiomyopathy, myocarditis or both, that arises as a result of an infection in a patient because Marumo et al (1990) teach that atrial natriuretic peptide (ANP) is present in the urine. It would be expected, absent evidence to the contrary, that a urine sample would be an appropriate sample to test for the presence of atrial natriuretic peptides.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same

way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known in the art that elevated levels of ANF are associated with chronic myocarditis . It is well known in the art to that urine is a source of atrial natriuretic peptides. Thus, it would be obvious to use a known products from known sources in a method of diagnosis cardiomyopathy, myocarditis or both that is ready for improvement to yield predictable results.

11. Claims 1-3, 5, 8-13 and 17-21 are rejected under 35 U.S.C. 103(a) as patentable over Lerman et al *(Lancet, May 1, 1993,Vol. 341, 1105-1109)* in view of Marumo et al *(Journal of Endocrinology, Oct. 1988, Vol. 119, Issue 1, p. 127-131)(Abstract only)*.

Independent claim 1 is directed to a method of assisting in the diagnosis of cardiomyopathy, myocarditis or both, that arises as a result of an infection in a patient, comprising, obtaining a sample of a body fluid from the patient, and determining a level of a brain natriuretic peptide (BNP) or fragment thereof, atrial natriuretic peptide (ANF) or fragment thereof, or both BNP and a fragment thereof and ANF or fragment thereof, within the sample of body fluid and comparing the level of BNP, ANF or both BNP and ANF to the level of BNP, ANF or both BNP and ANF from a control group, wherein an increase in the level of BNP, ANF or both BNP and ANF in the sample, compared to the

level of BNP, ANF or both BNP and ANF in the control group, is an indicator of a symptom of cardiomyopathy, mycarditis or both cardiomyopathy and mycarditis that arises as a result of an infection in a patient and dependent claim 5 is directed to the method of claim 1, wherein the body fluid is cerebrospinal fluid.

Lerman et al teach a method of determining atrial natriuretic peptide (ANP) levels in patients that are symptomless for left-ventricular dysfunction (see the Title and page 1105). Lerman et al teach that the left ventricle is an important determinant of the outcome of congestive heart failure (page 1105). Lerman et al teach that atrial natriuretic peptide is released as a C-terminal peptide and an N-terminal peptide (see page 1105). Lerman et al teach that plasma N-ANP concentrations are significantly increased in patients with symptomless left-ventricular dysfunction and that this peptide can serve as a marker for diagnosis of such patients (page 1105). Lerman et al teach that blood samples were taken from each patient and analyzed (page 1107). Lerman et al teach that antibodies to ANP $_{1-25}$ were used for assay of the N-terminal form and to the ANP $_{99-126}$ for assay of the C-terminal form (page 1107). Lerman et al teach assays were performed using radioimmunoassays (page 1107). Lerman et al teach that N-ANP measurement could be used to identify patients with symptomless heart disease and permit more in depth study of the natural history of congestive heart failure (page 1108).

Lerman et al do not teach the method of claim 1, wherein the body fluid is cerebrospinal fluid.

Marumo et al teach that atrial natriuretic peptide (ANP) is present in the cerebrospinal fluid (see the Abstract).

It would have been *prima facie* obvious at the time the invention was made to substitute the body fluid sample, plasma for the body fluid sample, cerebrospinal fluid in a method of assisting in the diagnosis of cardiomyopathy, myocarditis or both, that arises as a result of an infection in a patient because Marumo et al teach that atrial natriuretic peptide (ANP) is present in the cerebrospinal fluid. It would be expected, absent evidence to the contrary, that a cerebrospinal fluid sample would be an appropriate sample to test for the presence of atrial natriuretic peptides.

Additionally, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007), discloses that if a technique has been used to improve one composition and a person of ordinary skill would recognize that it would be used in similar compositions in the same way, using the technique is obvious unless its application is beyond that person's skill. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) also discloses that "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". It is well known in the art that elevated levels of ANF are associated with chronic myocarditis . It is well known in the art to that cerebrospinal fluid is a source of atrial natriuretic peptides. Thus, it would be obvious to use a known products from known sources in a method of diagnosis cardiomyopathy, myocarditis or both that is ready for improvement to yield predictable results.

Status of the Claims

12. No claims allowed.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Vanessa L. Ford/
Examiner, Art Unit 1645
March 12, 2008

/N. M. Minnifield/
Primary Examiner,
Art Unit 1645